

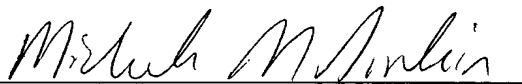
**REMARKS**

Applicants respectfully request that the foregoing amendments be made prior to examination of the present application. The amendments are made to correct multiple dependencies and do not change the scope of the invention.

Respectfully submitted,

Date April 11 2002

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By 

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**MARKED UP VERSION OF AMENDED APPLICATION****Marked up replacement paragraphs:**

Page 21, lines 7-19:

*E. coli* strain BL21 ( $\lambda$ DE3, *ompT*, *hsdS<sub>B</sub>* (*rb-mB-*), *gal*, *dcm*) was used as the host for the plasmids described below. Plasmid pKS1 contains a codon-optimised gene for the expression of the Hc fragment of TeNT under the control of the T7 promoter. It was created by PCR amplification (Pfu polymerase, Stratagene, Cambridge UK) of a 1357 bp fragment using pTETtac215 (Makoff *et al.*, 1989) as template and the oligonucleotides 5'GAGCATATGAAAAACCTTGAT (SEQ ID NO: 2) and 5'CGGATCCTTAGTCGTTGGTCCA (SEQ ID NO: 3) which introduce *NdeI* and *BamHI* sites at the 5' and 3' ends of the gene respectively. After blunt end ligation of the PCR product into the vector pCRScript (Stratagene) to form plasmid pJC6, the *NdeI* – *BamHI* fragment was purified by agarose gel electrophoresis using a Qiaex II gel purification kit (Qiagen, West Sussex, UK), and [subcloned]subcloned into pET28a (Novagen, Cambridge UK) which has previously been digested with *NdeI* and *BamHI* (Roche Molecular Biochemicals, East Sussex, UK). DNA manipulations were performed by standard procedures.

Page 22, table 1:

**TABLE 1 Mutants of TeNT Hc constructed**

Mutant Name	Oligonucleotides used for site directed mutagenesis
M5	NF38: 5' to 3' GGTGCGACTGGTACTTCTAAGGATCCGAATTCG (SEQ ID. NO:4) NF41: 3' to 5' CGAATTCGGATCCTTAGAAGTACCAGTCGCAACC (SEQ ID. NO:5)
T1308A	NP49: 5' to 3' GACTGGTACTTCGTTCCGGCTGATGAAGGTTGGA (SEQ ID. NO:6) NP50: 3' to 5' GGTCCAACCTTCATCAGCCGGAACGAAGTACCAG (SEQ ID. NO:7)
D1309A	NF51: 5' to 3' TGGTACTTCGTTCCGACCGCTGAAGGTTGGACGA (SEQ ID. NO:8) NF52: 3' to 5' CGTTGGTCCAACCTTCAGCGGTCGGAACGAAGTA (SEQ ID. NO:9)
E1310A	NF57: 5' to 3' TACTTCGTTCCGACCQATGCTGGTTGGACGCAACGAC (SEQ ID. NO:10) NF58: 3' to 5' GTCGTTGGTCCAACCAGCATCGGTCGGAACGAAGTA (SEQ ID. NO:11)
M13	NF47: 5' to 3' TTCGTTCCGACCGATGAATAAGGATCCGAATTCG (SEQ ID. NO:12) NF48: 3' to 5' CGAATTCGGATCCTTATTCATCGGTCGGAACGAA (SEQ ID. NO:13)
M28	NF79: 5' to 3' GGTACCCACAACGTGTCAGCGAACCGTGACATCCTG (SEQ ID. NO:14) NF80: 5' to 3' CAGGATGTCACGGTTCGGCTGACCGTTGTGGGTACC (SEQ ID. NO:15)

M37	NF81: 5' to 3' CTGGGTCTGGTTGGTACCAACGACCCGAACCGTGAC (SEQ ID. NO:16) NF82: 5' to 3' GTCACGGTTCGGGTCGTTGCTACCAACCAGACCGAG (SEQ ID. NO:17)
M40	NF79: 5' to 3' GGTACCCACAAGGTCAGCCGAACCGTGACATCCTG (SEQ ID. NO:18) NF80: 5' to 3' CAGGATGTCACGGTTCGGCTGACCGTTGTGGGTACC (SEQ ID. NO:19) and NF32: 5' to 3' CTTCTAACTGGTACTTCAACTCTCTGAAAGACAAAATCCTGGG (SEQ ID. NO:20) NF33: 3' to 5' CCCAGGATTTTGTCTTTCAGAGCGTTGAAGTACCAGTTAGAAG (SEQ ID. NO:21)
M58	NF91: 5' to 3' GTTGGTTACCCGAAACTGCAGAACCTGGACAGAATT (SEQ ID. NO:22) NF92: 3' to 5' AATTCTGTCCAGGTTCTGCAGTTTCGGGTAACAAC (SEQ ID. NO:23)
M564	NF32: 5' to 3' CTTCTAACTGGTACTTCAACTCTCTGAAAGACAAAATCCTGGG (SEQ ID. NO:24) NF33: 3' to 5' CCCAGGATTTTGTCTTTCAGAGCGTTGAAGTACCAGTTAGAAG (SEQ ID. NO:25)
M567	NF97: 5' to 3' CTAAGTGGTACTTCAACGCTCTGAAAGAGAAAAATCCTGGG (SEQ ID. NO:26) NF98: 3' to 5' CCCAGGATTTTGTCTTTCAGAGCGTTGAAGTACCAGTTAG (SEQ ID. NO:27)

Page 36, table 1:

Amino acid sequence of *C. tetani* neurotoxin (TeNT)

1	mpitinnfry	sdpvnndtii	mmeppyckgl	diyykafkit	driwivpery	efgtkpedfn
61	ppssliegas	eyydpnylrt	dsdkdrflqt	mvklfnrikn	nvagealldk	iinaipylgn
121	syslldkfdt	nsnsvsfnll	eqdpsgattk	samltnliif	gpgpvlnkne	vrqivlrvidn
181	knyfpcrdgf	gsimqmafcp	eyvptfdnvi	enitsltigk	skyfqdpall	lmhelihvlh
241	glygmqvssh	eiipskqey	mqhtypisae	elftfggqda	nlisidiknd	lyektlnndyk
301	aiannklsqvt	scndpnidid	sykqiyyqky	qfdkdsnggy	ivnedkfql	ynsimygfte
361	ielgkknfkn	trlsyfsnmh	dpvkipnll	dtiyndtegf	nieskdikse	ykgqnmrvnt
421	nafrnvdgsg	lvskliglck	kiipptnire	nlynrtaslt	dlggelciki	knedltfia
481	knsfseepfq	deivsyntkn	kplnfnyld	kiivdynlqs	kitlpndrtt	pvtkgipyap
541	eyksnaasti	eibhiddnti	yqylyaqksp	ttlqritmtn	svddalinst	kiysyfpsvi
601	skvnqgaqgi	lflqwvrdii	ddftnesssq	ttidkisdvs	tivpyigpal	nivkqgyegn
661	figalettg	vllleyipei	tlpviaalsi	aesstqkeki	iktidnflek	ryekwievky
721	lvkakwlgvt	ntqfqkrsg	myrsleyqvd	aikkiidyey	kiysgpdkeq	iadeinnlkn
781	kleekankam	ininifmres	srsflvngmi	neakkqllef	dtqsknilmq	yikanskfig
841	itelkiesk	inkvfstpip	fsysknlcdv	vdneedidvi	lkkstilnid	innndisdis
901	gfnssvityp	daqlvpging	kaihlvnnes	sevivhkamd	ieyndmfnnf	tvswlrvp
961	vsashlegyg	tneysiissm	kkhslsigsg	wsvslkgnnl	iwtlkdsage	vrqitfrdlp
1021	dkfnaylank	wvfititndr	lssanlying	vlmgsaeitg	lgairdnndi	tlklrcnnnn
1081	nqyvsidkfr	ifckalnpe	ieklytsyls	itflrdfwgn	plydteyyl	ipvassskdv
1141	qlkahtdytny	ltnapsytng	klniyyrrly	nglkfiikry	tpnneidsfv	ksgdfiklyv
1201	synnnehiyg	ypkdgnafnn	ldxilrvgyn	apgiplkkm	eavklrdikt	ysvqlklydd
1261	knasglvgvt	hngqigndpn	rdiliasnwy	fnhlkdkiig	cdwyfvpde	gwtnd

(SEQ ID NO: 1)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket No: 078883-0143

In re patent application of  
FAIRWEATHER, NEIL FRASER et al.  
Serial No. 10/018,997  
Filed: December 26, 2001  
For: TETANUS TOXIN POLYPEPTIDES

STATEMENT TO SUPPORT FILING AND SUBMISSION IN  
ACCORDANCE WITH 37 C.F.R. §§ 1.821-1.825

Assistant Commissioner for Patents  
Washington, D.C. 20231  
**Box SEQUENCE**

Sir:

In connection with a Sequence Listing submitted concurrently herewith, the undersigned hereby states that:

1. the submission, filed herewith in accordance with 37 C.F.R. § 1.821(g), does not include new matter;

2. the content of the attached paper copy and the attached computer readable copy of the Sequence Listing, submitted in accordance with 37 C.F.R. § 1.821(c) and (e), respectively, are the same; and

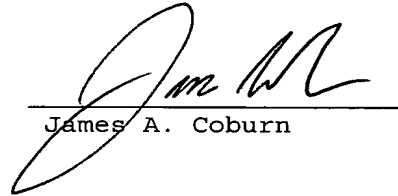
3. all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United

Serial No. 10/018,997

States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Respectfully submitted,

March 18, 2002  
Date

  
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